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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,792	11/10/2005	Giuseppe Pier Pelicci	LEDER-0014	4653

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EXAMINER	
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ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
10/31/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,792	PELICCI ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-23* is/are pending in the application.

4a) Of the above claim(s) *12-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-11* is/are rejected.

7)☒ Claim(s) *4,5 and 20-23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 2 and 4-23 are all the pending claims for this application.

2. Claim 3 was cancelled and Claims 1, 2, 4-8 and 11 were amended in the Response of 7/31/08.

3. Claims 12-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b).

4. Claims 1, 2, 4-11 and 20-23 are all the pending claims under examination.

5. Applicants have provided copies of references that raise new grounds for rejection.

Information Disclosure Statement

6. Copies of the patent documents (ref nos. 001 and 002) that were not provided with the IDS of 3/30/05 have now been provided with the Response of 7/31/08. The references have been entered in the attached PTO 892 from.

Withdrawal of Objections

Specification

7. The objection to the specification because it does not cross-reference the related applications and their dates of filing is withdrawn in view of the amendment to the specification to enter this information.

Claim Objections

8. The objection to Claim 7 for the apparent misspelling of "testosterone" is withdrawn in view of the amendment to correct the spelling.

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

9. The rejection of Claims 1-10 for the recitation "a treatment with an HDAC inhibitor is to be started/continued or not" is withdrawn in view of the deletion of the phrase from claim 1.

10. The rejection of Claims 1-8 for the recitation "a sample derived from tissue" in Claim 1 is withdrawn in view of the amendment of Claim 1 to replace "derived" with the term "obtained'.

11. The rejection of Claims 1-7, 9 and 10 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is withdrawn.

Applicants have amended Claim 1 to clarify the relationship between steps a) and b) of Claim 1 to describe the how the levels correlate with the treatability of the disorder.

12. The rejection of Claim 10 for the recitation "a further sample derived from tissue affected by the disorder which has been contacted with an HDAC inhibitor" is withdrawn in view of Applicants remarks on pp. 7-8 of the Response of 7/31/08.

Claim Rejections - 35 USC § 112, first paragraph

Biological Deposit

13. The rejection of Claims 4 and 5 under 35 U.S.C. § 112, first paragraph, because it is unclear if hybridoma cell lines which produce an antibody having the exact chemical identity of G2M-T25-H4ac and G2M-T52-ac have met the requirements under the Budapest Treaty (i.e., are known and publicly available) is withdrawn.

Applicants' specification identifies the DSMZ depository address for the two cell lines at pp. 8-9, restates the two deposits having been made with the DSMZ (pp. 12-13), and restates the DSMZ address and the date of deposit (9/24/02) along with the accession nos., ACC2578 and ACC2579, respectively, on p. 18. Applicants' have also provided deposit receipts for each of the hybridoma cell lines filed on 3/30/05.

Applicants have now made a statement of assurances that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application on p. 8 of the Response of 7/31/08.

Written Description/ New Matter

14. The rejection of Claims 20-23 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because Claims 20-23 are drawn to "antibody T25" and "antibody T52" or a conjugate is withdrawn.

Applicants have met the requirements of the Budapest Treaty as discussed above under section 13 to verify that a T25 and T52 antibody are available as of the filing date of the application.

Claim Rejections - 35 USC § 102

15. The rejection of Claims 1, 3, and 6-11 under 35 U.S.C. 102(a) as being anticipated by HEINZEL et al. (EP 02021228.8; filed 9/18/02; referred to as "EP '228") is withdrawn.

Applicants' comments that the HEINZEL reference is not a proper 102 reference is acknowledged.

Claim Rejections - 35 USC § 103

16. The rejection of Claims 1, 2, 6-9 and 11 under 35 U.S.C. 103(a) as being unpatentable over Butler et al. (Clin. Can. Res. 7:962-970 (2001); cited in the IDS of 3/30/05; Butler I) in view of Marks et al. (Nature Reviews Cancer 1:194-202 (2001); cited in the IDS of 3/30/05) is withdrawn.

Applicants' amendment of Claim 1 to incorporate the subject matter of Claim 3 for a monoclonal antibody overcomes the rejection.

17. The rejection of Claims 1 and 2 under 35 U.S.C. 103(a) as being obvious over Heinzel et al. (EP 02021228.8; filed 9/18/02; referred to as "EP '228") in view of Butler et al. (Clin. Can. Res. 7:962-970 (2001); cited in the IDS of 3/30/05) is withdrawn.

Applicants' comments that the HEINZEL reference is not a proper 102 reference is acknowledged.

Objections Maintained

Oath/Declaration

18. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It was not properly executed in accordance with either 37 CFR 1.66 or 1.68. The inventors listed as 201-203 and 205-207 on the oath/declaration of 11/10/05 have not properly executed the document because they have not provided the date of execution.

Applicants state on p. 7 of the Response that a supplemental Oath is enclosed but no copy of the document appears to have been filed. Applicants are invited to verify the absence of this filing on the public PAIR system.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. The rejection of Claims 9-11 and 20-23 for the recitation "a sample derived from tissue" in Claims 9-11 because the term "derived" is not clear within the meaning of processing the sample for determining histone acetylation is maintained.

The term "derived" has an art-recognized meaning as taking a material through a process in order to change a character (see attached Merriam-Webster on-line definition of "derived"). In order to examine the level of histone acetylation in a sample, would one of skill in the art need to process the material in some way in order to, for example, expose antigenic determinants for antibody binding?

Applicants have not responded to this aspect of the rejection in their Response.

20. The rejection of Claims 11 and 20-23 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps is maintained. See MPEP § 2172.01. The omitted steps are: the relationship between steps a) and b) of Claim 11. Is the histone acetylation level directly

correlated with the extent of the antibody binding to the sample in the contacting step of b) or is the antibody used to immunopurify the acetylated histone which level is then quantitated by some other means? Further it is not clear what is meant by the level of histone acetylation being "significantly lower" than the reference sample.

Applicants have not responded to this aspect of the rejection in their Response.

New Grounds for Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

21. Claims 1, 2, and 6-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Butler et al. (Clin. Can. Res. 7:962-970 (2001); cited in the IDS of 3/30/05; Butler I) in view of Marks et al. (Nature Reviews Cancer 1:194-202 (2001); cited in the IDS of 3/30/05) and Komatsu (US 20040198959; published 10/7/04; filed 3/13/02).

Claims 1, 2 and 6-10 are interpreted as being drawn to a method for diagnosing or prognosing a treatment for any disorder with an HDACi based on the level of histone acetylation in a sample derived from tissue affected by the disorder compared to the level in a reference sample where the level is determined by binding of acetylated histone to *any* monoclonal antibody specific to *any* acetylated histone and where a lower level of acetylation in the sample compared to the reference allows one to classify the disorder as being eligible for treatment with the HDACi (Claim 1), where Claim 2 is drawn to the method of Claim 1 where the antibody binds acetylated human histone 4 and the level of human histone H4 acetylation is determined, where the disorder is a condition associated with abnormal gene expression (Claim 6), where the disorders are listed in Claim 7, where the level of acetylation is determined by flow cytometry, immunochemistry, ELISA and/or Western Blot (Claim 8), where the reference sample is obtained from a tissue from a healthy individual where the tissue corresponds to the tissue affected by the disorder (Claim 9) and where the reference sample is a sample obtained from a tissue affected by the disorder where the tissue has been contacted with the HDACi.

Claim 11 is interpreted as being drawn to a method for classifying a tumor by contacting a sample obtained from a tissue affected by the tumor with an antibody that binds any acetylated histone but not to deacetylated histone, determining the level of acetylation based on the antibody interaction and classifying the tumor as to whether it should be treated with an HDACI based on whether the level of acetylated histone is significantly lower than a reference sample.

The claimed method was prima facie obvious at the time of the invention over Butler in view of Marks and Komatsu.

Butler describes methods of treating human prostate CWR22 xenograft tumors in mice with HDAC inhibitor, pyroxamide, where the excised tumor tissue sample is compared to vehicle control tumor tissue sample (reference), showed increased accumulated acetylation of histone by Western blot using polyclonal antibodies against acetylated histones H2A, H2B, H3 or H4 (p. 965, Col. 1, ¶ 3; Figure 6A; p. 966, Col. 2, ¶1). The antibodies of Butler recognize human histone H4 and are used to determine the level of acetylation of human histone H4 in the prostate cancer. The human prostate tumor of Butler would have been associated with abnormal gene expression. The level of human histone H4 acetylation was used to correlate the treatment effect of the HDACi against the vehicle control where Butler I teaches "the accumulation of acetylated histones may serve as a biological marker for the activity of HDAC inhibitor" (p. 967, Col. 1). Butler does not explicitly disclose that the level of histone acetylation would correlate with dosing in clinical trials whereas Marks describes on p. 197, Col. 2, last ¶ the occurrence of histone acetylation after HDAC treatment in normal and tumor cells and accumulation of acetylated histone is a useful marker of HDAC biological activity and can be used to monitor dosing in clinical trials (p. 199, Col. 2, ¶3).

Komatsu teaches using monoclonal antibodies recognizing acetylated residues in a protein regardless of the types of the adjacent amino acids, for histone proteins (e.g. histone H3), and more especially where detecting a state of histone acetylation under the influence of various stimulants can be detected by Western Blotting [0038]. The

ability of the monoclonal antibodies to bind acetylated histone H4 would be inherent to the antibodies of Komatsu, thus the claimed antibody appears to be the same as the prior art antibody. The Office does not have the resources to provide the factual evidence needed in order to establish that the prior art does not possess the same antibody, cells and methods as the claimed antibody and cells. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed compositions are different than those taught by the prior art and to establish patentable differences. See In re Best 562 F.2d 1252, 195 USPQ430 (CCPA 1977) and Ex Parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

It would have been prima facie obvious to have created the method invention in view of Butler and Marks and Komatsu. Butler and Marks disclose the use of histone acetylation as a marker for determining responsiveness to therapeutic agents, HDACi, in treating disorders, more especially prostate cancer. Both references disclose histone H3 and/or H4 as a preferred marker in assessing whether the extent of acetylation would correlate with tumor responsiveness to a drug, and that depending on the extent of acetylation, one could determine a clinical course of action, namely, monitoring the dose. Thus the combined method disclosures could have been considered by one of skill in the art as providing more than sufficient motivation to consider diagnosing or prognosing a treatment regimen for an HDAC inhibitor based on the level of human histone H3 or H4 acetylation using an antibody-based method of screening and especially using a clonotypic monoclonal antibody in view of Komatsu for recognizing acetylated residues on histone proteins. One skilled in the art would have been

reasonably assured of success in creating the method invention because the reagents for screening histone acetylation were already in existence and had already been shown to have specific binding activity in method assays for determining outcomes of HDACi therapy and continued course of treatment for specific disorders such as prostate cancer based on the combined reference disclosures of Butler and Marks and Komatsu. Butler and Marks and Komatsu rendered the claimed method invention prima facie obvious at the time of the invention.

Conclusion

19. No claims are allowed.

20. Claims 4, 5 and 20-23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643